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SKIN BLEACHING COMPOSITION

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SKIN BLEACHING COMPOSITION

Abstract of the Disclosure

A synergistic skin-bleaching composition for use by topical application has been found which comprises a mixture of a bleaching agent, a skin irritant-exfoliating agent and an anti-inflammatory agent formulated in a pharmaceutically-cosmetically acceptable vehicle. The composition comprising 2% hydroquinone, 0.05% retinoic acid and either 0.025% dexamethasone or fluorometholone was particularly effective.

Background of the Invention

1) Field of the Invention: This invention relates to a new synergistic skin-bleaching composition for use by topical application.

2) Description of the Prior Art: So-called compositions for the bleaching of skin have been known for many years, if not centuries. The prior art contains many references to the use of hydroquinone and its derivatives as agents in bleaching creams, etc., the most pertinent of which are:

a) U. S. Patent No. 3,060,097, issued October 23, 1962 to a skin-bleaching composition comprising sodium hypochlorite, hydroquinone monobenzyl ether and a "penetrant". Three British Patents No.'s 763,029, 855,431 and 965,869 issued to the same inventor on similar compositions.

b) French Patent No. 1,513,395, issued January 8, 1968 to a skin-bleaching composition comprising hydroquinone monobenzyl ether or a derivative thereof in combination with tyrothricin or a derivative thereof.

c) French Patent No. 1,270,854, issued July 24, 1961 to

1 a skin-bleaching composition comprising hydroquinone benzyl
2 ether (1'ether de benzylhydroquinone) and an anti-oxidant.
3 The product may be formulated to contain vitamins, amino
4 acids, cholesterol, etc.

5 d) United States Patents No. 's 2,274,725 (March 30, 1942),
6 2,376,884 (May 29, 1945) and 2,377,188 (May 29, 1945) are to sun-
7 screen preparations comprising hydroquinone as the active sun-
8 filter agent. These preparations are stabilized by the addition
9 of certain anti-oxidants.

10 e) Zschr. Haut-Geschl.-Krkh. 42, 17: 711-716 reports
11 studies of bleaching the skin using hydroquinone monobenzyl
12 ether. When a subject was found to have sensitive skin, 5%
13 hydroquinone monobenzyl ether and 4% prednisolone was used to
14 prevent or control the contact dermatitis produced by the hydro-
15 quinone monobenzyl ether. No mention is made of an improved
16 bleaching effect when the preparation contained prednisolone.

17 f) Some other articles reporting on skin-bleaching by the
18 use of hydroquinone or its derivatives are:

- 19 1. Archives of Dermatology, 84, No. 1, 131-134 (July
20 1961).
- 21 2. Clinical Medicine, 70, No. 6, 1111-1114 (June 1963).
- 22 3. Clinical Medicine, 72, No. 3, 87-88 (March 1966).
- 23 4. Postgraduate Medicine, 37, No. 2, 198-201 (February
24 1965).
- 25 5. J. Investigative Medicine, 18, 119-135 (1952).
- 26 6. J. Am. Medical Assoc., 152, No. 7, 577-582 (June
27 13, 1953).
- 28 7. Dermatologica, 134, 125-128 (1967).
- 29 8. Archives of Dermatology, 93, No. 5, 589-600 (May
30 1966).

1 The above cited art constitutes but a small portion of the
2 prior art but is representative of that deemed most pertinent.
3 None of the above teaches or anticipates the three component,
4 synergistic compositions of the present invention.

5
6 Summary of the Invention

7 A synergistic skin-bleaching composition for external appli-
8 cation has been found comprising a bleaching agent selected from
9 the group comprising hydroquinone, hydroquinone monomethyl ether,
10 hydroquinone monoethyl ether and hydroquinone monobenzyl ether,
11 a skin irritant-exfoliating agent and an anti-inflammatory cor-
12 ticosteroid.

13 Complete Disclosure

14 It has long been desirable in certain skin disorders or
15 diseases to be able to depigment (bleach) the skin to remove
16 certain disfiguring blemishes generally caused by the deposi-
17 tion of excess quantities of melanin. This hyperpigmentation
18 is generally viewed as cosmetically undesirable or psychologi-
19 cally disabling. Examples of these blemishes would be freckles,
20 senile lentigo, lentigines (liver spots), melasma, contact
21 allergy pigmentation, sunburn pigmentation, post-inflammatory
22 hyperpigmentation due to abrasion, burns, wounds, dermatitis,
23 phototoxic reaction and other similar small, fixed pigmented
24 lesions. Likewise, it is also desirable to be able to decolorize
25 normally pigmented skin to generally increase "fairness" of
26 appearance and to blend hypopigmented areas into surrounding
27 bleached skin. This is particularly so in the treatment of
28 negroes, brown-skin people, or generally dark skinned people
29 suffering from vitiligo.

30 It was an object of the present invention to prepare an

1 effective and superior product as compared to those currently
2 on the market or known in the literature.

3 ~~The compounds hydroquinone, hydroquinone monomethyl ether,~~
4 ~~hydroquinone monobenzyl ether, ammoniated mercury, zinc peroxide,~~
5 ~~red mercuric oxide, sodium hypochlorite, hydrogen peroxide, mer-~~
6 ~~curous chloride and bichloride of mercury are all known in the~~
7 ~~literature as bleaching agents of the skin. Only hydroquinone~~
8 ~~is recognized as a bleaching agent possessing satisfactory~~
9 ~~qualities.~~

10 The object of the present invention has been achieved by the
11 formulation of a superior synergistic skin-bleaching composition
12 for external application which comprises a mixture of a bleaching
13 agent, a skin irritant-exfoliating agent and an anti-inflammatory
14 agent in a pharmaceutically-cosmetically acceptable vehicle.

15 A preferred embodiment of the present invention is a syner-
16 gistic skin-bleaching composition for external application com-
17 prising ~~a bleaching agent selected from the group comprising~~
18 ~~hydroquinone, hydroquinone monomethyl ether, hydroquinone mono-~~
19 ~~ethyl ether and hydroquinone monobenzyl ether, a skin irritant-~~
20 ~~exfoliating agent and an anti-inflammatory corticosteroid for-~~
21 ~~mulated in a pharmaceutically-cosmetically acceptable vehicle.~~

22 Another preferred embodiment is a synergistic skin-bleaching
23 composition for external application comprising about 1% to about
24 10% of a bleaching agent selected from the group comprising hydro-
25 quinone, hydroquinone monomethyl ether, hydroquinone monoethyl
26 ether and hydroquinone monobenzyl ether, and about 0.025% to about
27 80% of a skin irritant-exfoliating agent and about 0.01% to about
28 3.0% of an anti-inflammatory corticosteroid formulated in a phar-
29 maceutically-cosmetically acceptable vehicle.

30 Another preferred embodiment is a synergistic skin-bleaching

1 composition for external application comprising about 1% to
 2 about 5% of a bleaching agent selected from the group comprising
 3 hydroquinone, hydroquinone monomethyl ether, hydroquinone mono-
 4 ethyl ether and hydroquinone monobenzyl ether, about 0.025% to
 5 about 15% of a skin irritant-exfoliating agent selected from
 6 the group comprising unsaturated fatty acids, long chain fatty
 7 acid esters or salts thereof, retinoic acid, oleic acid, arachi-
 8 donic acid, polyoxyethylene lauryl or myristyl ethers, alkyl-
 9 amines containg 5 to 16 carbon atoms, salicylic acid and benzoic
 10 acid, and about 0.01% to about 3.0% of an anti-inflammatory
 11 corticosteroids selected from the group comprising hydrocorti-
 12 sone, cortisone, prednisolone, prednisone, dexamethasone, beta-
 13 methasone, fluocinolone acetonide, triamcinolone, fluocinolone,
 14 triamcinolone acetonide, methylprednisolone, fluorometholone,
 15 or an ester thereof when chemically possible, formulated in a
 16 pharmaceutically-cosmetically acceptable vehicle.

17 A more preferred embodiment is a synergistic skin-bleaching
 18 composition for external application comprising about 1% to about
 19 5% of hydroquinone, about 0.020% to about 10% of a skin irritant-
 20 exfoliating agent selected from the group comprising retinoic
 21 acid, arachidonic acid, oleic acid, linoleic acid, linolenic
 22 acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate,
 23 polyoxyethylene lauryl ether, polyoxyethylene myristyl ether,
 24 salicylic acid, benzoic acid, and n-octylamine, and about 0.01% to
 25 about 3% of an anti-inflammatory corticosteroid selected from the
 26 group comprising dexamethasone, betamethasone, fluocinolone, flu-
 27 cinolone acetonide, triamcinolone, hydrocortisone, triamcinolone,
 28 acetonide, fluorometholone, or an ester thereof when chemically possible,
 29 formulated in a pharmaceutically-cosmetically acceptable vehicle.

30 A most preferred embodiment is the synergistic skin-bleaching

1 composition for external application comprising about 2% hydro-
2 quinone, about 0.05% retinoic acid and about 0.025% fluorometholone
3 formulated in a pharmaceutically-cosmetically acceptable vehicle

4 Another most preferred embodiment is the synergistic skin-
5 bleaching composition for external application comprising about
6 2% hydroquinone, about 0.05% retinoic acid and about 0.025%
7 dexamethasone formulated in a pharmaceutically-cosmetically
8 acceptable vehicle.

9 Still another most preferred embodiment is the synergistic
10 skin-bleaching composition for external application comprising
11 about 2% hydroquinone, about 0.05% retinoic acid and about 2.5%
12 hydrocortisone or hydrocortisone acetate formulated in a phar-
13aceutically-cosmetically acceptable vehicle.

14 A preferred embodiment of the present invention is a method
15 of bleaching human skin by applying to the skin a synergistic
16 skin-bleaching composition which comprises a mixture of a bleaching
17 agent, a skin irritant-exfoliating agent and an anti-inflammatory
18 agent formulated in a pharmaceutically-cosmetically acceptable
19 vehicle.

20 Another preferred embodiment is the method of bleaching
21 human skin wherein the bleaching composition comprises a
22 bleaching agent selected from the group comprising hydroquinone,
23 hydroquinone monomethyl ether, hydroquinone monomethyl ether and
24 hydroquinone monobenzyl ether, a skin irritant-exfoliating agent
25 and an anti-inflammatory corticosteroid formulated in a phar-
26aceutically-cosmetically acceptable vehicle.

27 A further preferred embodiment is the method of bleaching
28 human skin wherein the bleaching composition comprises about 1%
29 to about 10% of a bleaching agent selected from the group com-
30prising hydroquinone, hydroquinone monomethyl ether, hydroquinone

1 monoethyl ether and hydroquinone monobenzyl ether, and about 0.025%
 2 to about 80% of a skin irritant-exfoliating agent and 0.01% to about
 3 3.0% of an anti-inflammatory corticosteroid formulated in a pharma-
 4 ceutically-cosmetically acceptable vehicle.

5 A more preferred embodiment is the method of bleaching human
 6 skin wherein the bleaching composition comprises about 1% to about
 7 5% of a bleaching agent selected from the group comprising hydroquinone,
 8 hydroquinone monoethyl ether, hydroquinone monoethyl ether and hydro-
 9 quinone monobenzyl ether, about 0.025% to about 15% of a skin irri-
 10 tant-exfoliating agent selected from the group comprising unsaturated
 11 fatty acids, long chain fatty acid esters or salts thereof, retinoic
 12 acid, arachidonic acid, polyoxyethylene lauryl or myristyl ethers,
 13 oleic acid, alkylamines containing 5 to 16 carbon atoms, salicylic
 14 acid and benzoic acid, and about 0.1% to about 3.0% of an anti-
 15 inflammatory corticosteroids selected from the group comprising
 16 hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone,
 17 betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone,
 18 triamcinolone acetate, methylprednisolone, fluorometholone, or an
 19 ester thereof when chemically possible, formulated in a pharmaceu-
 20 tically-cosmetically acceptable vehicle.

21 Another more preferred embodiment is the method of bleaching
 22 human skin wherein the bleaching composition comprises about 1% to
 23 about 5% of hydroquinone, about 0.020% to about 10% of a skin irri-
 24 tant-exfoliating agent selected from the group comprising retinoic
 25 acid, arachidonic acid, linoleic acid, oleic acid, linolenic acid,
 26 sodium lauryl sulfate, dioctyl sodium sulfosuccinate, polyoxy-
 27 ethylene lauryl ether, polyoxyethylene myristyl ether, salicylic
 28 acid, benzoic acid, and n-octylamine, and about 0.01% to about
 29 3% of an anti-inflammatory corticosteroid selected from the group
 30 comprising dexamethasone, betamethasone, fluocinolone, fluocinolone

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1 acetone, triamcinolone, hydrocortisone, triamcinolone acetate,
2 fluorometholone, or an ester thereof when chemically possible,
3 formulated in a pharmaceutically-cosmetically acceptable vehicle.

4 A most preferred embodiment is the method of bleaching
5 human skin wherein the bleaching composition comprises about
6 2% hydroquinone, about 0.05% retinoic acid and about 2.5%
7 hydrocortisone or hydrocortisone acetate formulated in a phar-
8 maceutically-cosmetically acceptable vehicle.

9 A most preferred embodiment is the method of bleaching
10 human skin wherein the bleaching composition comprises about
11 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluoro-
12 metholone formulated in a pharmaceutically-cosmetically acceptable
13 vehicle.

14 Another most preferred embodiment is the method of bleaching
15 human skin wherein the bleaching composition comprises about 2%
16 hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone
17 formulated in a pharmaceutically-cosmetically acceptable vehicle.

18 Hydroquinone, hydroquinone monomethyl ether and hydro-
19 quinone monobenzyl ether are all known in the literature as
20 bleaching agents for lightening of the skin. While there is
21 some question as to the mode of action of these agents and treat-
22 ment is considered an "art" rather than a science, it is generally
23 thought that all of these agents work through the common inter-
24 mediate hydroquinone. Additionally, it is known that hydro-
25 quinone is the least irritating of these hydroquinones, the
26 ethers generally having the reputation of causing various types
27 of dermatitis. It is also known that the ethers are unpredictable
28 in their bleaching effect and sometimes cause a progression of
29 depigmentation after application has been stopped. Hydro-
30 quinone is the agent of choice when a hydroquinone bleaching

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1 agent is desired for these reasons.

2 A 2% hydroquinone composition is commercially available
3 under the trademark Eldoquin and Eldopaqua by Paul Elder &
4 Company. Hydroquinone is reported to be the sole active in-
5 gredient.

6 In our hands, it has been found that a preparation con-
7 taining only 2% hydroquinone is unpredictable and not always
8 effective. Similar results have been reported in the literature
9 (Clinical Medicine, 72, No. 3, 87-88 [March 1966]) wherein 35%
10 of those subjects treated showed excellent results, 5% good,
11 35% fair and 25% poor.

12 Subsequent investigations to improve these results were
13 undertaken and it has been unexpectedly found that a composition
14 containing hydroquinone, or a derivative thereof, in combination
15 with a skin irritant-exfoliating agent and an anti-inflammatory
16 corticosteroid produced good to excellent results in almost all
17 of the subjects so treated. One must consider these results to
18 be a type of synergism inasmuch as these superior results can
19 not be achieved by any of the individual components alone.

20 The compositions of the present invention are applied
21 according to the following general regimen: In the case of
22 the formulation of example 1, the composition was applied two
23 to three times daily to the areas to be bleached. The composi-
24 tion is preferably applied three times a day for two days, then
25 two times a day till irritation (mild inflammation) can be seen.
26 Depending upon the degree of irritation, the composition is applied
27 once or twice a day till depigmentation occurs. Depigmenta-
28 tion usually begins to occur five to twenty-one days after the
29 initial application. Depigmentation is usually complete within
30 six to ten weeks.

In patients with recurrent hyperpigmentation (negroes, other dark-skinned races), pigmentation can be maintained by several applications per week.

The results produced by the application of the above composition are exceptionally good. In almost 100% of the subjects so treated, good to excellent depigmentation was obtained. The results were particularly dramatic in normal negro skin, wherein the skin was bleached white in the majority of subjects so treated.

Generally, similar results can be obtained with any of the formulations of the present inventions, although the frequency of application, the time required for depigmentation and the degree of depigmentation will vary with the components strength, and pharmaceutical vehicle used.

Examples of the Embodiments

Example 1

Hydroquinone	2%
Retinoic Acid	0.05%
Fluorometholone	0.025%
Fragrance q.s.	
Propylene glycol	
Ethanol (95%) H ₂ O q.s. ad 100 ml.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone and dissolve in about 80 ml. of the 50:50 mixture of propylene glycol and ethanol. Add the fragrance and q.s. ad to 100 ml. Mix well and apply to area to be bleached.

Example 2

Substitution in the formula of example 1 for the fluoro-

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metholone used therein of 0.025% of dexamethasone produces an equivalent formulation.

Example 3

Hydroquinone	2%
Retinoic acid	0.05%
Fluorometholone	0.025%
Vanishing Cream base q.s. ad 100 gm.	

Finally pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the vanishing cream base and mix well to obtain a gritless paste. Add additional vanishing cream base to make 100 gm. of product. Mix well and apply.

Example 4

Hydroquinone	2%
Retinoic acid	0.05%
Fluorometholone	0.025%
Emollient lotion q.s. ad 100 ml.	

Finally pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the emollient lotion to the powder to make a gritless paste. Add sufficient lotion to make 100 ml. Mix well and apply.

Example 5

Hydroquinone	2%
Retinoic acid	0.05%
Hydrocortisone	2.5%
Vanishing cream base q.s. ad 100 gm.	

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Prepare as in example 3.

Example 6

Hydroquinone	2%
n-Octylamine	0.5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Finally pulverize the hydroquinone and fluorometholone.
Add the n-octylamine and a small quantity of vanishing cream to make a gritless paste. Add sufficient vanishing cream to make 100 gm. Mix well and apply.

Example 7

Hydroquinone	2%
Sodium lauryl sulfate	5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in example 3.

Example 8

Hydroquinone	2%
Linoleic acid	50%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95 %) q.s. ad 100 ml.	

Prepare as in example 1.

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Example 9

2	Hydroquinone	2%
3	Linolenic acid	55%
4	Fluorometholone	0.025%
5	Propylene glycol	
6	Ethanol (95%) BA q.s. ad 100 ml.	

8 Prepare as in example 1.

Example 10

11	Hydroquinone	2%
12	Arachidonic Acid	10%
13	Fluorometholone	0.025%
14	Propylene glycol	
15	Ethanol (95%) BA q.s. ad 100 ml.	

17 Prepare as in example 1.

Example 11

20	Hydroquinone	2%
21	Polyoxyethylene lauryl ether	10%
22	Fluorometholone	0.025%
23	Propylene glycol	
24	Ethanol (95%) BA q.s. ad 100 ml.	

26 Prepare as in example 1.

Example 12

29	Hydroquinone monobenzyl ether	5%
30	Retipic acid	0.05%

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1 Fluorometholone 0.025%

2 Vanishing cream base q.s. ad 100 gm.

3
4 Prepare as in example 3.

5 Example 13

6
7 Hydroquinone 5%

8 Retinoic acid 0.05%

9 Fluorometholone 0.05%

10 Vanishing cream base q.s. ad 100 gm.

11
12 Prepare as in example 3.

13
14 The above examples are illustrative of some of the variations
15 in formulation that can be made within the scope of the present
16 invention.

17 To prepare a more elegant or stable product, it may be de-
18 sirable to incorporate fragrances, pigments, preservatives and/or
19 a stabilizer including anti-oxidants, all of which are within the
20 ability of those knowledgeable in the art.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A synergistic skin-bleaching composition for external application which comprises a mixture of about 1% to about 10% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monethyl ether and hydroquinone monobenzyl ether; about 0.025% to about 10% of retinoic acid as a skin irritant-exfoliating agent, and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid, formulated in a pharmaceutically-cosmetically acceptable vehicle.

2. A composition of claim 1 comprising about 1% to about 5% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monomethyl ether and hydroquinone monobenzyl ether, about 0.025% to about 10% of retinoic acid and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid selected from the group comprising hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

3. A composition of claim 1 comprising about 1% to about 5% of hydroquinone, about 0.020% to about 10% of retinoic acid as an skin-irritant-exfoliating agent, and about 0.01% to about 3% of an anti-inflammatory corticosteroid selected from the group comprising dexamethasone, betamethasone, flucinoline, flucinolone acetonide, triamcinolone, hydrocortisone, triamcinolone acetonide, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

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4. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluorometholone formulated in a pharmaceutically-cosmetically acceptable vehicle.

5. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone formulated in a pharmaceutically-cosmetically acceptable vehicle.

6. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and about 2.5% hydrocortisone or hydrocortisone acetate formulated in a pharmaceutically-cosmetically acceptable vehicle.

7. A composition as in claim 1 or 2 comprising hydroquinone, retinoic acid, and an anti-inflammatory corticosteroid.



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